hyperreactivity. This amendment is supported by, for example, pages 2 (lines 9-14), 15 (lines 27-29), 16 (lines 6-7), 26 (line 7) and 31 (lines 3-11). New dependent claims 32-36 have also been added and claims 5, 18 and 19 have been amended. Claims 5, 32, 33, 34, 35, 36, 18, 19 and 20 are of a parallel structure to claims 2, 27, 4, 28, 29, 30, 6, 7 and 8.

An Appendix including a marked-up copy of the amendments is attached, showing the changes. The attachment is captioned **"Version with markings to show changes made."** Former claims 2-26 are rejected under 35 USC §§ 112, 102 and 103. For the reasons outlined below, these rejections are respectfully traversed and reconsideration and withdrawal are respectfully requested.

Rejections Under 35 USC § 112

Claims 2-26 of record stand rejected under 35 USC §112, first paragraph, on the grounds that the specification does not provide a written description supporting the use of homologs, analogs, fragments or derivatives of CGRP other than mammalian Calcitonin Gene Related Peptide (CGRP), adrenomedullin and the linear analog, [Cys(ACM)^{2,7}] CGRP.

Solely in order to expedite prosecution of the instant application, Applicant has amended the instant claims to recite mammalian Calcitonin Gene Related Peptide (CGRP), and the linear analog, [Cys(ACM)^{2,7}] CGRP, thereby rendering this rejection moot.

Claims 2-26 of record stand rejected further under 35 USC §112, first paragraph, on the grounds that the specification does not provide enabling support for a method for *prevention* of disease, but merely for treatment of disease.

Solely in order to expedite prosecution of the instant application, the claims have been amended to recite only treatment of disease, and not prevention, thereby rendering this rejection moot.

Applicant reserves the right to pursue any subject matter removed by these amendments in one or more continuation applications.

Rejections Under 35 USC § 102

The Examiner has rejected claims 2-26 pursuant to 35 USC § 102(e) as anticipated in light of United States Patent No. 5,858,978 as evidenced by *The Merck Manual*. Applicant respectfully disagrees and submits the following.

To summarize briefly, the '978 Patent describes a relationship (observed ***in vitro***) between CGRP and an inhibition of release of a cytokine from macrophages, via a cAMP-mediated mechanism. In view of the wide-ranging role of cytokines in the body, the '978 Patent then speculates as to a lengthy list of disorders that might be treated with CGRP.

The possible utilities mentioned in the '978 patent are extremely wide ranging. For instance, in column 5 of the '978 patent, the following diseases or conditions are recited:

- pain, fever, etc. following acute traumatic injuries or surgery;
- viral diseases e.g. human influenza or canine distemper;
- chronic inflammatory diseases such as edema, or in the joints or urinary tract;
- arthritis, bursitis, tendonitis;
- lupus, rheumatoid arthritis, scleroderma;
- allergic reactions e.g. penicillin reaction; etc.

Even more far reaching uses are mentioned in column 13:

- reducing inflammation after organ transplant, surgery, etc.
- treating mental problems;
- treating headaches and earaches;
- preventing tooth loss; and
- preventing pregancy and preventing fetus rejection.

In brief, the '978 patent provides a lengthy list of disorders or conditions with which cytokines such as IL-1 may be involved. Within this list, allergic reactions involving the lungs (asthma) are mentioned at col. 13 line 18.

The '978 patent also recites generic information concerning the formulation and use of pharmaceutical compositions containing CGRP in columns 6-8. Within the

discussion of how CGRP might be administered into the respiratory tract (eg. in a spray, mist, or aerosol), asthma is mentioned merely as an example of a disorder in which respiratory tract administration would be preferred (col. 7, lines 45-49).

Hence, the '978 patent recites a laundry list of wide-ranging conditions or disorders that CGRP might be used to treat, together with a discussion of how pharmaceutical compositions may be formulated for a wide range of desired modes of administration. The most explicit reference in the '978 patent to asthma is merely in the context of an example of the kind of disorder in which inhalation-type administration of a pharmaceutical composition is preferred.

In the absence of any guidance in the '978 patent that CGRP could specifically be used to treat asthma (e.g. by way of working examples showing the treatment of asthma or symptoms thereof), the skilled person could not reasonably be expected to pick through the various and diverse teachings of the '978 patent to arrive at the conclusion that CGRP is useful for the treatment of asthma. Without further guidance, the skilled person would be at a loss to determine, as amongst the plethora of different diseases and conditions recited, which if any could realistically be treated with CGRP.

Applicant respectfully submits that the class of disorders, routes of administration and pharmaceutical compositions described in the '978 patent are not sufficiently limited or well delineated to anticipate the presently amended claims. One of ordinary skill in the art could not be able to "at once envisage" the specific combination of CGRP and asthma, as presently claimed, in the '978 patent, as required for a finding of anticipation. See *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990).The recitation in the '978 patent of a vast number of diseases or conditions, pharmaceutical compositions and modes of drug administration does not "describe" and therefore does not anticipate the treatment of asthma with CGRP as presently claimed. See *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

In other words, the skilled person, confronted with the '978 patent, could not "see the trees for the forest" in view of the large number of diverse diseases mentioned in the reference. Applicant submits that such a teaching does not constitute anticipation. See *Fujikawa v. Wattanasin* (39 USPQ2d 1895), quoting in part from *In re Ruschig* (154 USPQ 118):

> It is an old custom in the woods to mark trails by making blazemarks on the trees. It is no help in finding a trail ... to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

Reconsideration and withdrawal of the rejection of the claims under 35 USC §102(e) over the '978 patent are therefore respectfully requested.

Rejections Under 35 USC § 103

Claims 2-26 stand rejected under 35 USC §103(a) as obvious in light of the '978 Patent discussed above in view of United States Patent No. 5, 510, 339 to Gleich et al.

Applicant respectfully submits that Gleich et al. fail to cure the above-discussed deficiencies in the teachings of the '978 patent. As discussed in detail below, neither the '978 patent nor Gleich et al. nor a combination thereof provide any reasonable expectation of success that CGRP could successfully be used to treat asthma as presently claimed. Applicant reiterates that the '978 Patent only describes a relationship (observed ***in vitro)*** between CGRP and an inhibition of IL-1 release from macrophages, via a cAMP-mediated mechanism. As noted in applicant's letter of December 4, 2000, numerous differences exist between the subject matter disclosed in the '978 Patent and the findings described in the instant application. First, applicant notes that the focus of the '978 patent is the accumulation of giant cells during inflammation. In contrast, inflammation linked to asthma is not characterized by an accumulation of giant cells and the mediators responsible for giant cell-related chronic inflammation are not the same as those associated with asthma.

Further, the '978 patent notes that "cytokines are very potent with diverse biological activities which affect nearly every organ when administered *in vivo*" (column 4, lines 11-14), suggesting that any particular activity of such a cytokine cannot be predicted by one skilled in the art, given the great diversity of the activities potentially associated with it. This is clear when the nature of the *hypothesized* disorders said to be treatable using CGRP listed in the '978 patent (some of which are listed above) are considered, which are as far ranging as canine distemper, mental problems, gingivitis and

the use of CGRP as an oral contraceptive. Given the considerable variation in the mechanisms of such disorders, Applicant respectfully submits that one of skill in the art would clearly not have a reasonable expectation of success in treating any of these diseases, and would certainly not be guided to choose any one in particular to try.

Further, the applicant refers to the Examiner's reference to the *The Merck Manual* as evidence of the novelty objection above, which leads to the assumption that the Examiner considers the information presented in *The Merck Manual* to reflect the general common knowledge of the art. In this regard, applicant notes that *The Merck Manual* also indicates, as is indeed generally known in the art, that CGRP is known to cause bronchoconstriction and airway obstruction (oedema, mucus secretion, etc.; see page 557, right column, last paragraph), which was in fact the state of the knowledge in the art prior to the instant Applicant's findings. The instant Applicant, in contrast, was the first to directly test the effects of CGRP on animal airways and thus discovered that its effects were precisely opposite to the conventional wisdom in the art. Therefore, *The Merck Manual* directly teaches against a use of CGRP for the treatment of asthma.

Further, conflicting results have been shown with regard to CGRP activity. As such, in the absence of direct measurements of the effects of CGRP on airways challenged with various stimuli as performed by the instant inventor, the state of the art prior to the instant invention provides no guidance to one skilled in the art that CGRP may be used effectively for such a purpose.

In light of the above, Applicant concludes that the state of the art would not provide a reasonable expectation of success to one of skill in the art, with regard to the use of CGRP for the treatment of asthma. Therefore, applicant respectfully requests that the objection be withdrawn.

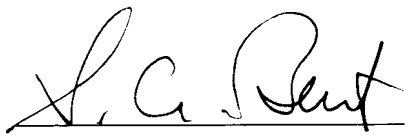
Other Issues

During the telephone interview of December 11, 2001, Examiner Nolan raised the issue of the article "Cadieux *et al.* (1999) Am. J. Respir. Crit. Care Med., 159:235-243" (item A30 of the Information Disclosure Statement). Specifically, Examiner Nolan noted that the authorship of this article is not identical to the applicants listed in the instant

application, and requested the filing of a "Katz" declaration. Therefore, please find enclosed a further Declaration pursuant to 37 CFR 1.132 (incorrectly labelled as "37 CFR 1.131"), which establishes that Alain Cadieux is the sole inventor of the subject matter disclosed in the just noted article.

It is believed this responds to all of the Examiner's concerns, however if the Examiner has any further questions, he is invited to contact David Schwartz (Reg. No. 48,211) at 613-232-2486. Further, If the Examiner does not consider that the application is in a form for allowance, an interview with the Examiner is respectfully requested.

Respectfully submitted,



July 26, 2002
Date

Stephen A. Bent
Attorney for Applicant
Patent Office Reg. 29,768

Please address correspondence to:

FOLEY & LARDNER
Washington Harbour
3000 K Street N.W., Suite 500
Washington, D.C. 20007-5109
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

VERSION WITH MARKINGS TO SHOW CHANGES MADE

4. (Once amended) The method of claim [3]21, wherein said active agent is selected from the group consisting of human CGRP and rat CGRP.

5. (Once amended) The method of claim [4]31, wherein said administration is via a pulmonary route.

6. (Once amended) The method of claim [3]21, wherein said active agent has a purity of at least about 95 to 98%.

7. (Once amended) The method of claim [3]21, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

18. (Once amended) The method of claim [15]31, wherein said active agent has a purity of at least about 95 to 98%.

19. (Once amended) The method of claim [15]31, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

21. (Once amended) A method for the treatment of [a disease selected from] asthma, [bronchospastic diseases characterized by airway hyperreactivity, and lung inflammatory diseases characterized by increased eosinophilia,] wherein said method comprises the administration of an active agent selected from the group consisting of mammalian calcitonin gene-related peptide (mammalian CGRP)[, adrenomedullin] and mammalian [Cys(ACM)^{2,7}]CGRP.